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TEMPORAL AND OTHER EXPOSURE ASPECTS OF RESIDENTIAL MAGNETIC FIELDS MEASUREMENT IN RELATION TO ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN: THE NATIONAL CANCER INSTITUTE/CHILDREN'S CANCER GROUP STUDY

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INVITED PAPER

Abstract — Case–control studies have used a variety of measurements to evaluate the relationship of children's exposure to magnetic fields (50 or 60 Hz) with childhood leukaemia and other childhood cancers. In the absence of knowledge about which exposure metrics may be biologically meaningful, studies during the past 10 years have often used time-weighted average (TWA) summaries of home measurements. Recently, other exposure metrics have been suggested, usually based on theoretical considerations or limited laboratory data. In this paper, the rationale and associated preliminary studies undertaken are described as well as feasibility and validity issues governing the choice of the primary magnetic field exposure assessment methods and summary metric used to estimate children's exposure in the National Cancer Institute/Children's Cancer Group (NCI/CCG) case–control study. Also provided are definitions and discussion of the strengths and weaknesses of the various exposure metrics used in exploratory analyses of the NCI/CCG measurement data. Exposure metrics evaluated include measures of central tendency (mean, median, 30th to 70th percentiles), peak exposures (90th and higher percentiles, peak values of the 24 h measurements), and measurements of short-term temporal variability (rate of change). This report describes correlations of the various metrics with the time-weighted average for the 24 h period (TWA-24-h). Most of the metrics were found to be positively and highly correlated with TWA-24-h, but lower correlations of TWA-24-h with peak exposure and with rate of change were observed. To examine further the relation between TWA and alternative metrics, similar exploratory analysis should be considered for existing data sets and for forthcoming measurement investigations of residential magnetic fields and childhood leukaemia.

INTRODUCTION

Since the initial report by Wertheimer and Leeper[(1)] linking residential magnetic field exposure with childhood cancer, subsequent case-control studies have used a variety of exposure assessment methods to evaluate the relationship of children's residential magnetic field (50 or 60 Hz) exposures with leukaemia and other childhood cancers[(2)]. In the absence of supportive laboratory evidence identifying potential carcinogenic mechanisms or biologically meaningful indices, it has been reasonably assumed that magnetic flux density was the appropriate measure to evaluate. Many questions remain, however, as to which exposure metric, if any, is the most appropriate one[(3)]. To date, the indirect measures of magnetic flux density employed as surrogate estimates of children's dose have included residential wire codes, magnetic fields measured in homes, historically calculated residential field levels, measurements of distance between homes and nearby power lines, and personal dosimetry[(3)]. Although the earliest residential magnetic field measurements consisted of spot or other short-term measurements, more recently 24 h residential measurements have been obtained and summarised using the time-weighted average (TWA)[(4–7)].

Detailed evaluation of the temporal patterns of the 24 h residential magnetic field measurements has suggested that TWA fails to capture many aspects of the widely ranging temporal variability of residential magnetic field levels. A variety of alternative metrics have been proposed[(2,8)] that incorporate potentially meaningful aspects of the temporal variability, including other measures of central tendency, peak exposures, short-term temporal variability and others. Some of the proposed alternative metrics, their definitions, strengths and

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weaknesses are presented in Table 1. To date, there has been limited evaluation of either the rationale for utilising TWA as a summary measure or that for various alternative metrics within the context of case-control studies of childhood cancer and magnetic field exposure.

In this paper, important considerations in relation to metrics that could be utilized in residential magnetic field measurements studies are examined. The rationale is described as well as the methods and results of preliminary investigations to identify a feasible and valid exposure assessment approach for the National Cancer Institute and Children's Cancer Group (NCI/CCG) case-control study[4,9]. In addition, the various alternative metrics assessed in a recent exploratory analysis are considered and the correlations among the alternative metrics in a residentially stable subset of the NCI/CCG study population are evaluated.

THE NCI/CCG STUDY AND ITS PRIMARY EXPOSURE METRIC FOR MEASURED RESIDENTIAL MAGNETIC FIELDS

The detailed methodology and results of the NCI/CCG study have been described elsewhere[4,9] Briefly, the study included 629 children with acute lymphoblastic leukaemia (ALL) who were under 15 years of age and were registered with the CCG and 619 controls who were ascertained by random digit dialing. For the subject's current and former homes in which he/she resided during the five years immediately prior to the reference date (the date of diagnosis for each case and the date that the corresponding matched case was diagnosed for each control), magnetic flux density was measured using a standardised protocol involving EMDEX-C meters (Electric Field Measurements, West Stockbridge, MA). For each eligible residence, the final measurement protocol consisted of a 24 h measurement in the child's bedroom; 30 s spot measurements in the child's bedroom, kitchen and family room; if appropriate, a 30 s measurement in the room in which the mother slept during the index pregnancy; and a 30 s measurement within 0.9 m (3 ft) outside the front door. The subjects' summary magnetic field exposure for each home was calculated from the weighted average of the room measurements according to the child's age[9], the weights being derived from activity diary data

Table 1. Characteristics of selected alternative temporal metrics of residential magnetic field measurements evaluated in the NCI/CCG study.

Metric	Definition	Strengths	Weaknesses
TWA (24 h)	A weighted mean of 24 h measurement in the child's bedroom and spot measurements in the other rooms multiplied by duration resided in each residence (at least with a 24-h measurement)[4,9].	Well correlated with personal contemporaneous measurements (obtained using personal dosimetry in small US studies)[10,11]; captures information about the magnitude and persistence of magnetic field exposure; used widely.	Ignores temporal pattern of exposure delivery
TWA (10 pm–6 am)	Calculated as TWA but incorporating only for sleep-time period of the 24 h measurement[6]	Same as 24 h TWA but may approximate more closely exposures of children who spend little time in their bedroom except to sleep	Same as 24 h TWA but poorer estimate for children spending higher proportion of time in bedroom during time periods other than sleep time
Middle percentiles	Median, 30th–70th percentiles of exposure	Reflect more stable levels, not as dependent on transient peak levels	Ignores peaks and temporal variability
Measures of extreme exposure	Highest levels of exposure, 90th–100th percentiles	May capture exposure from electric appliances	No biological basis to support any chronic effects; difficult to study because of lack of detailed time specific data
Measures of short-term variability or rate of change	The amount of change in the steady-state flux density for data discretely sampled at short intervals over time; metric reflects the short-term intermittency of the magnetic field[14]	Potential physiological effects based on limited laboratory data	Limited laboratory data assessing effects; transients were not measured in the NCI/CCG study

(recording subjects' locations according to room or yard at home, and detailed location information if away from home) collected in two personal measurement studies[10,11]. The primary measure of exposure for each study subject was an average of the summary level for all the eligible measured homes, weighted according to the duration of residence. Both the final measurement protocol and the summary exposure metric used to estimate each subject's exposure were derived from several preliminary studies described immediately below.

PRELIMINARY STUDIES CONDUCTED TO DETERMINE THE MEASUREMENT PROTOCOL AND PRIMARY METRIC EMPLOYED IN THE NCI/CCG STUDY

Survey of electric power companies

Information was sought about the availability and types of historical utility company records that could be used as adjunct to residential measurements in order to estimate children's residential magnetic field levels. The possibility was also evaluated of estimating children's past residential exposure by using electrical consumption information derived from both utility company records and monthly residential bills from previous years. Both of these efforts were undertaken to identify alternative information that could be routinely collected for all study subjects and used in place of in-home measurements when access was refused to current or former homes of subjects. A standardised questionnaire was developed to assess engineering features, other characteristics, and location of power lines in relation to nearby residences from more than 200 electrical power companies serving the nine-state geographic study region evaluated in the NCI/CCG study. An important reason to collect this information was to determine whether the Wertheimer–Leeper power line classification system would be applicable in the many different locations included in the nine-state study area. This classification system is a surrogate indicator for residential magnetic field exposure, which uses visual assessment of power lines near homes to estimate the magnetic field level in homes. Based on initial inquiries, it was learned that it was not possible to obtain recent or historic current load data for distribution lines (e.g. the types of power lines closest to most US homes) since no US company collects or maintains such information. It was also found that neither household electric consumption information from utility company records nor monthly residential bills received by families were systematically filed and/or stored by most companies or families, respectively, and neither provided useful surrogate information to substitute for residential measurements or wire codes. However, the survey revealed that it would be feasible to utilise the Wertheimer–Leeper classification scheme for wire coding throughout the study region, since engineering features, other characteristics, and location of power lines in relation to nearby homes were similar throughout the many geographic locations in the nine states included in our study.

Personal measurement studies

Two personal measurement studies were carried out among 29 young children (ages 0–8) from volunteer families in the Washington, DC, metropolitan area and among 64 control children (ages 0–14) enrolled in the NCI/CCG study. The objectives were to (1) examine the relationship between area measurements (including the 24 h children's bedroom and spot measurements in other rooms) and personal dosimetry for estimating children's individual magnetic field levels; (2) clarify the contribution and importance of school, daycare or other away from home exposures to children's personal magnetic field exposures in the 24 h interval; (3) identify a subset of residential, school and/or daycare area measurements that best approximate children's exposures; and (4) ascertain variability of behaviour in relation to magnetic field exposure by age. The details of the measurement protocols and the results of these studies have been described elsewhere[10,11]. Briefly, both personal measurement studies revealed that the most variable component of children's exposure to magnetic fields was from residential settings rather than from school, daycare or other away from home exposures, and that the residential measurements were good predictors of total exposure. Each of these studies found a good correlation between the 24 h bedroom measurements and at-home personal dosimetry. Detailed evaluation of controls from the nine-state study region showed that 24 h bedroom measurements were good predictors of personal exposure for both younger ($r=0.76$) and older ($r = 0.72$) children[11]. Both measurement studies revealed very poor correlations of children's summary 24 h personal exposure with school, daycare or other away from home measurements[10,11]. Based on these results, as well as the extensive difficulties encountered in obtaining access to schools and daycare centres, it was concluded that the importance and additional value of assessing away from home exposure to residential magnetic fields were limited, because away from home exposures contributed little to 24 h personal exposure and access to schools and/or daycare centres would be expensive and available for only a small proportion of subjects. Since school and/or daycare exposures often change throughout the day and from year to year, the predictive value of post-diagnosis measurements would be uncertain.

Discussion with paediatric oncologists

Our discussions with several paediatric oncologists suggested that cancer treatments frequently altered children's activities in general, and, in particular, in relation to use of electrical appliances and proportion of time spent in various rooms in their home, school, and other settings. Most of the paediatric oncologists agreed that differences between pre-diagnostic and post-diagnostic daily activities and, in particular, amount of time spent at home could result in substantial misclassification of residential magnetic field exposures if personal dosimetry measurements obtained post-diagnosis were used to estimate magnetic field levels pre-diagnosis. Data from our personal dosimetry studies also revealed that children spent less time at home or in their bedroom with increasing age. Based on all of this information, it was concluded that contemporaneous personal dosimetry data were unlikely to provide valid exposure estimates in the NCI/CCG study.

Seasonal variability study

A pilot study was undertaken to examine how well a single measurement visit during an arbitrary time of day, day of week and season can estimate longer term residential magnetic field levels[12]. The study population included 51 randomly selected controls and subjects of similar age identified using the same telephone sampling strategy from two cities in the nine-state study area of the NCI/CCG study. Repeated measurements were made in the residences of these subjects approximately every two months during a one-year period using the same measurement protocol employed in the NCI/CCG study. The results revealed a small seasonal effect estimated to account for a very small variability among measurements in a given home. There was no evidence for a day of week effect. No difference was found between measurements taken on weekends and weekdays. A small, but statistically significant diurnal effect was observed.

EXPLORATORY EVALUATION AND COMPARISONS OF TIME-WEIGHTED AVERAGE AND OTHER ALTERNATIVE TEMPORAL METRICS FROM THE NCI/CCG STUDY

To examine how closely the TWA correlated with various alternative metrics, the exploratory analyses focused on a subset of the NCI/CCG cases and controls. The subset included 904 subjects (478 cases and 426 controls) who resided for 70% or more of the 5-year period immediately prior to diagnosis or reference date in one home in which a 24 h child's bedroom measurement and spot measurements were obtained in specified rooms and immediately outside the front door. A small number of these subjects (N = 56) also lived in additional home(s) which have 24 h measurements for very small proportions of the 5-year period. Eight otherwise eligible subjects were excluded from the analysis because of missing covariates. An important rationale for limiting the exploratory analysis of alternative temporal metrics to this subset was to avoid complexities in combining and interpreting temporal components of 24 h measurements across houses. The analysis was also restricted to the residentially most stable subjects, because subjects residing in more than one residence often did not have 24 h bedroom measurements obtained in all homes included in the summary metric.

For this subset of subjects, the risks of ALL according to the time-weighted average summary 60 Hz residential magnetic fields level for the entire 24 h period (TWA-24-h) and for the sleep-time period (TWA-10 pm–6 am) using various categorical subdivisions and unconditional logistic regression[13] are shown in Tables 2(a–c). The same cut-points (<0.065 μT, 0.065–0.099 μT, 0.100–0.199 μT and >0.200 μT) used in our initial report[4] are shown in Table 2(a). In Tables 2(b) and 2(c), respectively, results are depicted using standard percentiles employed in other case-control studies of residential magnetic field exposure and childhood cancer (0–49th, 50–74th, 75–89th, and 90th percentile or higher in Table 2(b)) and using quartiles (Table 2(c)). In each of the three tables, all estimates of risk have been adjusted for the age of the subject at the reference date, the subject's sex, the mother's education level, and family income. Overall, regardless of the cut-points used, risks were slightly higher for the sleep-time period (10 pm–6 am) than for the entire 24 h interval. Compared with risks observed in unconditional logistic regression analyses of the entire study population (629 cases versus 619 controls)[4], risks were slightly lower for the subset of more residentially stable subjects shown in Tables 2(a–c), although the confidence intervals overlapped substantially.

Table 3(a) summarises the characteristics of the magnetic field levels (mean, standard deviation, minimum, maximum) for the selected alternative temporal exposure metrics evaluated. The mean values for 24 h and sleep-time TWAs were similar (0.11 μT and 0.10 μT respectively). The 24 h mean peak value was higher (0.36 μT) than that of the sleep-time mean peak level (0.22 μT). Risk estimates for childhood ALL derived from exploratory analysis using these alternative metrics are currently in preparation and will be presented elsewhere (A. Auvinen, personal communication).

Table 3(b) shows the correlations among different metrics for magnetic field levels. For all subjects, most of the metrics were positively and highly correlated. The results did not vary by case-control status (data not shown). As seen in the table, the patterns were similar both for the 24 h measurement period and the sleep-time period (10 pm–6 am). However, the correlations were lower between TWA-24-h and peak exposure (r = 0.57). When 8 subjects were excluded, whose peak for the 24 h period was >0.22 μT but whose TWA-24-h was <0.10 μT, the new correlation coefficient between TWA-24-h and peak 24-h increased (r = 0.71). The most extreme peaks tended to occur during the daytime. At night, the peaks were similar to the 24-h TWA resulting in a relatively high correlation (r = 0.73).

Table 2. Risk of childhood acute lymphoblastic leukaemia according to time-weighted average summary levels of 60 Hz residential magnetic fields in a subset of the NCI/CCG study.

(a)

Magnetic-field levels (μT) Categories	Cases*	Controls*	OR† (95% CI)
TWA (24 h)			
<0.065 μT	210	209	1.00
0.065–0.099 μT	90	73	1.14 (0.79–1.66)
0.100–0.199 μT	112	95	1.18 (0.84–1.66)
>0.200 μT	66	49	1.25 (0.82–1.93)
TWA (10 pm–6 am)			
<0.065 μT	226	220	1.00
0.065–0.099 μT	87	75	1.06 (0.73–1.54)
0.100–0.199 μT	107	87	1.19 (0.84–1.68)
>0.200 μT	58	44	1.19 (0.76–1.86)

(b)

Magnetic-field levels (μT) Categories by percentiles	Cases*	Controls*	OR† (95% CI)
TWA (24 h)			
0–49th percentile (<0.070 μT)	229	219	1.00
50–74th percentile (0.070–0.127 μT)	124	104	1.10 (0.79–1.52)
75–89th percentile (0.128–0.228 μT)	73	63	1.11 (0.75–1.64)
90th percentile or higher (>0.228 μT)	52	40	1.16 (0.73–1.85)
TWA (10 pm–6 am)			
0–49th percentile (<0.065 μT)	226	220	1.00
50–74th percentile (0.065–0.119 μT)	126	103	1.13 (0.81–1.57)
75–89th percentile (0.120–0.209 μT)	73	65	1.10 (0.74–1.63)
90th percentile or higher (>0.209 μT)	53	38	1.25 (0.78–2.00)

(c)

Magnetic-field levels (μT) Categories by quartiles	Cases*	Controls*	OR† (95% CI)
TWA (24 h)			
Q1 (<0.044 μT)	120	120	1.00
Q2 (0.044–0.070 μT)	113	101	1.06 (0.72–1.54)
Q3 (0.071–0.128 μT)	122	103	1.13 (0.78–1.64)
Q4 (>0.128 μT)	123	102	1.14 (0.79–1.66)
TWA (10 pm–6am)			
Q1 (0.42 μT)	115	118	1.00
Q2 (0.042–0.065 μT)	117	105	1.10 (0.76–1.60)
Q3 (0.066–0.120 μT)	122	104	1.13 (0.78–1.65)
Q4 (>0.120 μT)	124	99	1.22 (0.83–1.78)

*Analysis was restricted to 904 subjects (478 cases and 426 controls) who each lived in one home for 70% or more of the 5-year period immediately prior to diagnosis or reference date with a 24 h child's bedroom measurements and spot measurements in various rooms and/or outside the front door. A small number of these subjects (N = 56) also lived in additional home(s) which have 24 h measurements for a small proportion of the 5 year period. Eight subjects with missing covariates were excluded from the analysis.

†OR was adjusted for child's age at reference date, child's gender, mother's education and family income.

Table 3. (a) Mean, minimum and maximum values of selected exposure metrics for measured magnetic field levels (60 Hz) (n=904 subjects).

Exposure metric	Magnetic field level (μT)			
	Mean	SD	Minimum	Maximum
TWA (24 h)	0.11	0.11	0.02	1.29
TWA (10 pm–6 am)	0.10	0.11	0.02	1.47
Mean child's bedroom, 24 h	0.11	0.12	0.01	1.60
Mean child's bedroom (10 pm–6 am)	0.10	0.12	0.01	1.89
30th percentile, 24 h	0.08	0.09	0.01	1.18
30th percentile (10 pm–6 am)	0.08	0.11	0.01	1.99
50th percentile, 24 h	0.10	0.11	0.02	1.30
50th percentile (10 pm–6 am)	0.09	0.12	0.01	2.00
70th percentile, 24 h	0.12	0.15	0.02	2.00
70th percentile (10 pm–6 am)	0.11	0.14	0.01	2.01
90th percentile, 24 h	0.16	0.23	0.02	3.89
90th percentile (10 pm– 6am)	0.14	0.21	0.02	3.89
95th percentile, 24 h	0.18	0.25	0.02	3.89
95th percentile (10 pm–6 am)	0.15	0.22	0.02	3.89
99th percentile, 24 h	0.22	0.30	0.02	3.94
99th percentile (10 pm–6 am)	0.18	0.25	0.02	3.94
Peak (100th percentile) 24 h	0.36	0.55	0.02	6.06
Peak (100th percentile) (10 pm–6 am)	0.22	0.32	0.02	4.03

Table 3. (b) Correlation coefficients (r) between time-weighted average and other alternative temporal metrics for the measured magnetic field levels in the NCI/CCG study.

Exposure metric	All subjects (n = 904)	
	TWA (24 h)	TWA (10 pm–6 am)
TWA (24 h)	1.00	0.97
TWA (10 pm–6 am)	0.97	1.00
Mean child's bedroom, 24 h	0.97	0.95
Mean child's bedroom (10 pm–6 am)	0.92	0.97
30th percentile, 24 h	0.93	0.90
30th percentile (10 pm–6 am)	0.86	0.93
50th percentile, 24 h	0.94	0.90
50th percentile (10 pm–6 am)	0.88	0.94
70th percentile, 24 h	0.93	0.93
70th percentile (10 pm–6 am)	0.89	0.93
90th percentile, 24 h	0.85	0.83
90th percentile (10 pm– 6am)	0.81	0.82
95th percentile, 24 h	0.84	0.81
95th percentile (10 pm–6 am)	0.82	0.83
99th percentile, 24 h	0.82	0.78
99th percentile (10 pm–6 am)	0.81	0.81
Peak (100th percentile) 24 h	0.57	0.54
Peak (100th percentile) (10 pm–6 am)	0.73	0.72
Rate of change, 30 s–24 h	0.54	0.51
Rate of change, 30 s (10 pm–6 am)	0.52	0.51

DISCUSSION

Although some of the preliminary studies carried out to evaluate feasibility and validity issues governing the choice of the primary exposure assessment measurement protocol and metric used to summarize the measurement data in the NCI/CCG study have been described earlier, the entirety of preliminary studies are here reviewed. Absence of historical current load data for distribution lines (the power lines closest to most US homes) as well as absence of information about the power line voltage corresponding to specific nearby residences precluded use of calculated historical fields. It was found that the household electric consumption information from utility company records and monthly residential bills received by families were not systematically filed and/or stored; therefore neither provided useful surrogate information to substitute for residential measurements or wire codes. However, the survey of more than 200 electrical power companies revealed that it would be feasible to utilise the Wertheimer–Leeper classification scheme for wire coding throughout the nine-state study locations. Personal measurement studies demonstrated that residential exposures were highly correlated with, and were the most variable components of, children's total 24 h exposures. In contrast, school exposures in our nine-state US study region were poorly correlated with children's 24 h personal exposures. Also, the personal measurement studies revealed that access to schools would be difficult, if not prohibited, for a high proportion of children. In addition, the variability in magnetic field levels in different areas within schools would increase costs for estimating summary exposures across relevant classrooms and would make it difficult to use contemporaneous personal measurements to extrapolate to past exposures (since subjects would have been in different classrooms as well as different schools at earlier ages). Discussion with paediatric oncologists indicated that changes in behaviour (in relation to time spent in the residence and to use of electrical appliances) between pre-diagnostic and post-diagnostic time periods would limit the validity of contemporaneous personal dosimetry in estimating children's past magnetic field exposures.

Use of TWA as a summary metric was only recently incorporated in epidemiologic studies of residential magnetic field levels and childhood cancer following the advent of longer term measurements of 24 h or more[4–6]. To date, there have been few attempts to examine the growing number of alternative metrics that have been proposed. In one study, Michaelis *et al*[6] evaluated the sleep-time component of the 24 h measurement and found a non-significant four-fold increase in childhood leukaemia risk (odds ratio, OR = 3.9, 95%CI (confidence interval) 0.9–16.9) for the median of the magnetic field during the night. Risks of childhood leukaemia in the NCI/CCG study were observed to be slightly higher for the sleep-time period than for the entire 24 h interval, but it was also found that the mean values of the entire 24 h and the sleep-time TWAs were very highly correlated (r = 0.98) and the ORs were similar for the 24 h and the sleep-time measurements.

In relation to alternative metrics, most of them were positively and highly correlated with TWA. The high degree of correlation among the alternative metrics and TWA suggests that childhood ALL risk estimates derived from metrics other than TWA would most likely be similar to those obtained using the primary TWA metric. Nevertheless, it would be useful to evaluate the various alternative metrics in existing data sets (with 24 h or longer residential measurements) and in forthcoming measurement investigations of residential magnetic fields and childhood leukaemia. In the absence of information about which exposure metrics may be biologically meaningful, further evaluation of epidemiological studies offers the only opportunity to further our understanding about any association of residential magnetic field exposures with childhood leukaemia.

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